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Five-Year National Surveillance of Invasive Candidiasis: Species Distribution and Azole Susceptibility from the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study

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ABSTRACT Data on the epidemiology of invasive candidiasis (IC) and the antifungal susceptibility of *Candida* isolates in China are still limited. Here we report on surveillance for IC from the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study. Sixty-five tertiary hospitals collected 8,829 *Candida* isolates from 1 August 2009 to 31 July 2014. Matrix-assisted laser desorption ionization–time of flight mass spectrometry supplemented by ribosomal DNA sequencing was used to define the species, and the fluconazole and voriconazole susceptibilities were determined by the Clinical and Laboratory Standards Institute disk diffusion method. A total of 32 *Candida* species were identified. *Candida albicans* was the most common species (44.9%), followed by the *C. parapsilosis* complex (20.0%), *C. tropicalis* (17.2%), and the *C. glabrata* complex (10.8%), with other species comprising $<$3% of isolates. However, in candidemia, the proportion of cases caused by *C. albicans* was only 32.3%. *C. albicans* and *C. parapsilosis* complex isolates were susceptible to fluconazole and voriconazole ($<$6% resistance), while fluconazole and azole cross-resistance rates were high in *C. tropicalis* (13.3% and 12.9%, respectively), *C. glabrata* complex (18.7% and 14%, respectively), and uncommon *Candida* species (44.1% and 10.3%, respectively) isolates. Moreover, from years 1 to 5 of the study, there was a significant increase in the rates of resistance to fluconazole among *C. glabrata* complex isolates (12.2% to 24.0%) and to both fluconazole (5.7% to 21.0%) and voriconazole (5.7% to 21.4%) among *C. tropicalis* isolates ($P < 0.01$ for all comparisons). Geographic variations in the causative species and susceptibilities were noted. Our findings indicate that antifungal resistance has become noteworthy in China, and enhanced surveillance is warranted.

KEYWORDS invasive candidiasis, epidemiology, antifungal susceptibility, fluconazole, voriconazole, China

Received 6 April 2018 **Returned for modification** 23 April 2018 **Accepted** 3 May 2018

Accepted manuscript posted online 9 May 2018

Citation Xiao M, Sun Z-Y, Kang M, Guo D-W, Liao K, Chen SC-A, Kong F, Fan X, Cheng J-W, Hou X, Zhou M-L, Li Y, Yu S-Y, Huang J-J, Wang H, Xu Y-C, on behalf of the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study Group. 2018. Five-year national surveillance of invasive candidiasis: species distribution and azole susceptibility from the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study. J Clin Microbiol 56:e00577-18. https://doi.org/10.1128/JCM.00577-18.

Editor David W. Warnock

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Invasive candidiasis (IC) is a life-threatening disease with high rates of morbidity and mortality, especially among immunocompromised and critically ill patients (1, 2). Worldwide, *Candida albicans* remains the predominant pathogen causing IC, but the prevalence of infection due to non-*albicans Candida* species is on the rise, with non-*albicans Candida* species accounting for over 50% of cases of IC in many geographic regions (1, 3). Of note, non-*albicans Candida* species are often more resistant to antifungal drugs than *C. albicans* (2, 4), which is concerning with respect to clinical outcomes.

Early and appropriate therapy in IC is essential to improve the overall outcomes (5–7). However, initiation of such targeted antifungal therapy is contingent on the timely diagnosis of IC. Because rapid IC diagnostic assays, such as molecular-based tests, have not yet reached the bedside in many hospitals, most clinicians still rely on insensitive culture-based methods to direct patient management (1, 7). Robust local epidemiological data, including knowledge of antifungal susceptibility profiles and trends, are therefore essential for the selection of initial antifungal therapy (1–4). This hinges upon effective surveillance networks.

The China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study was the first and has continued to be the largest national surveillance program for invasive fungal infections, including IC, in mainland China. Initiated in 2009 (8), over 8,000 isolates were collected during the first to fifth surveillance years. We have previously reported results from limited surveillance or on the epidemiology relevant to selected species (9–14) but not the overall results from the entire CHIF-NET study. Here we provide a perspective on the overall comparative species distribution of *Candida* pathogens and azole antifungal susceptibility data for *Candida* isolates collected during the first 5 years of the study.

MATERIALS AND METHODS

The CHIF-NET study. The CHIF-NET study is a prospective, laboratory-based, multicenter study of invasive yeast infections, including IC, initiated in 2009 (as described above). Each surveillance year began on 1 August of the year and continued to 31 July of the following year. Sixty-five tertiary general hospitals from 27 provinces in China participated in the first 5 years (Fig. 1). The number of participating hospitals increased from 12 in the first year to 22, 22, 48, and 61 in the second to fifth years, respectively.

The study inclusion criteria were as previously described (8). In each surveillance year, all *Candida* isolates from eligible patients with IC were forwarded to the central laboratory, Department of Clinical Laboratory, Peking Union Medical College Hospital, for species confirmatory identification and antifungal susceptibility testing. The study was approved by the Human Research Ethics Committee of the Peking Union Medical College Hospital (S-263).

Species identification. To ensure the accuracy of identification, all invasive *Candida* isolates were identified to the species level in the central laboratory. In year 1 of the study, isolates were identified by DNA sequencing of the fungal ribosomal DNA internal transcribed spacer (ITS) regions (8), and isolates from years 2 to 5 were identified by a combination of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), using a Vitek MS system (bioMérieux, Marcy l'Étoile, France), supplemented by ITS sequencing (15).

Antifungal susceptibility testing. Susceptibility to fluconazole and voriconazole was determined using the Clinical and Laboratory Standards Institute (CLSI) M44-A2 disk diffusion method (16). For all isolates from all years, species-specific MIC clinical breakpoint (CBP) interpretive criteria were applied to *C. albicans*, *Candida tropicalis*, the *Candida parapsilosis* complex, the *Candida glabrata* complex, and *Candida krusei* according to the guidelines in the reference CLSI M60 document (17), while the susceptibilities of the other *Candida* species were interpreted in accordance with the CLSI M44-S3 document guidelines (18). The quality control strains were *C. albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, and *Candida krusei* ATCC 6258.

Statistical analysis. All comparisons were performed using SPSS software (version 12.0; SPSS Inc., Chicago, IL, USA). Comparisons of continuous variables were performed by using the Mann-Whitney test, and comparisons of categorical variables were performed by using a chi-square test or Fisher's exact test, as appropriate. A *P* value of 0.05 was significant.

RESULTS

Demographics. A total of 8,829 nonrepetitive (i.e., nonduplicate) *Candida* isolates from separate patients were collected; 37.8% of the isolates were cultured from male patients, and 62.2% of the isolates were cultured from female patients. The patients' ages ranged from 0 to 103 years (median, 50 years; interquartile range, 45 to 72 years).

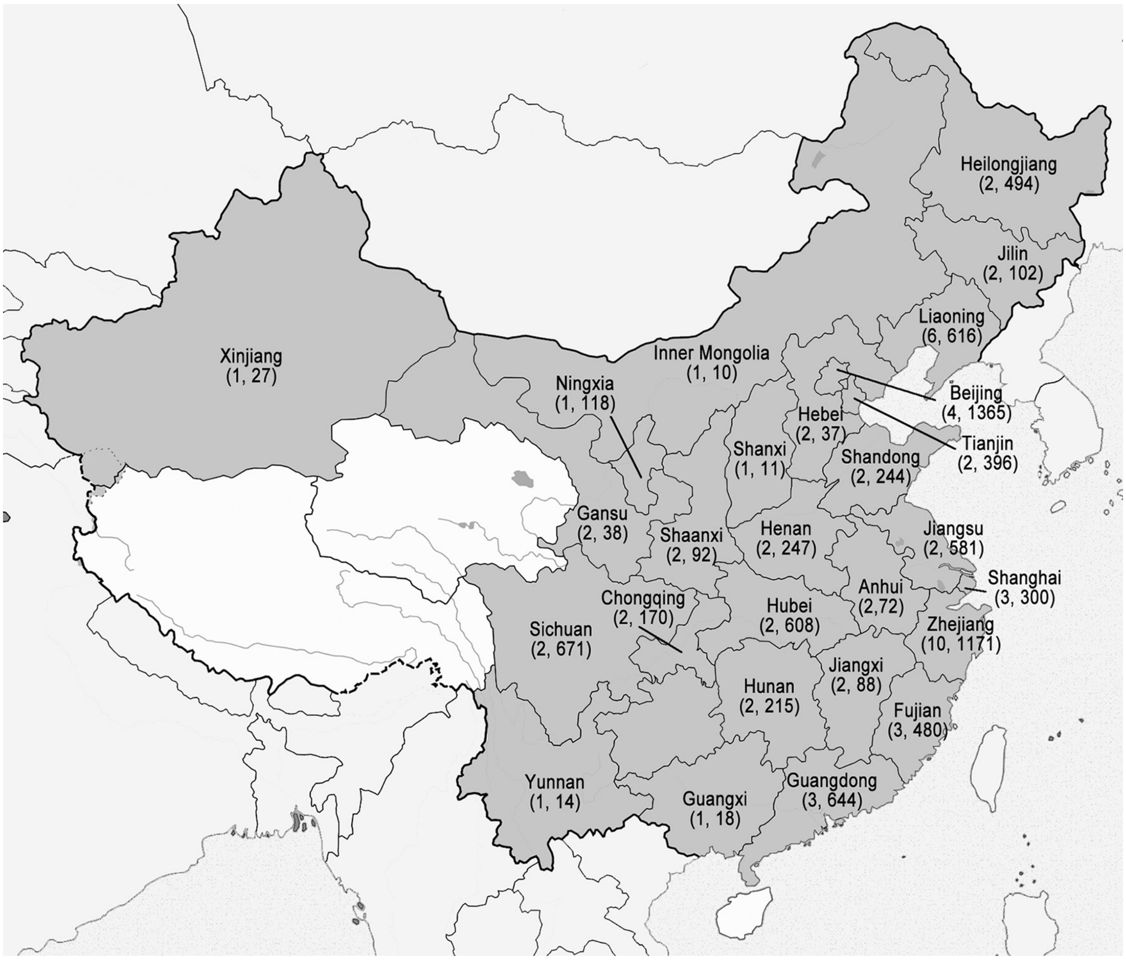


FIG 1 Geographic regions of the CHIF-NET study covered (27 provinces, in dark gray). The first number in parentheses under the province name indicates the number of hospitals that participated in the CHIF-NET study in each province, and the second number indicates the number of isolates collected.

***Candida* species.** Thirty-two species of *Candida* were identified among the 8,829 isolates. *C. albicans* was the most common (3,965 isolates, 44.9%), with no significant trend in frequency being observed over the 5 years ($P > 0.05$) (Table 1). Non-*albicans Candida* species accounted for 4,864 (55.1%) isolates (Table 1). Of these, *C. parapsilosis* complex isolates were the most frequent 1,762 (20.0%) and consisted of *C. parapsilosis sensu stricto* (1,526/8,829 isolates, 17.3%), *Candida metapsilosis* (1.9%), and *Candida orthopsilosis* and *Lodderomyces elongisporus* (0.4% each; Table 1). *C. tropicalis* was the third most common species (1,515 isolates, 17.2%), followed by the *C. glabrata* complex (955 isolates, 10.8%); of the latter, 98.5% were *C. glabrata sensu stricto* isolates ($n = 941$), while *Candida nivariensis* and *Candida bracarensis* were rare (0.1% and <0.1%, respectively; Table 1). Other species were rare (<2.1%; Table 1). No significant trends in frequency were seen for non-*albicans Candida* species ($P > 0.05$ for all comparisons).

Species distribution according to specimen type. Of the various specimen types, over 40% of invasive *Candida* isolates (3,858/8,829 isolates, 43.7%) were recovered from blood, followed by ascitic fluid (20.8%), pus (10.4%), central venous catheter tips (CVC; 8.0%), bile (4.6%), bronchoalveolar lavage fluid (4.1%), pleural fluid (3.9%), cerebrospinal fluid (1.8%), and tissue (1.4%) (Fig. 2).

The proportion of non-*albicans Candida* isolates recovered from blood cultures (2,612/3,858 isolates, 67.7%) was significantly higher than that recovered from other specimen types (2,252/2,719 isolates, 45.3%) ($P < 0.01$) (Fig. 2). More specifically, the difference in the relative proportion was the largest for *C. parapsilosis* complex isolates

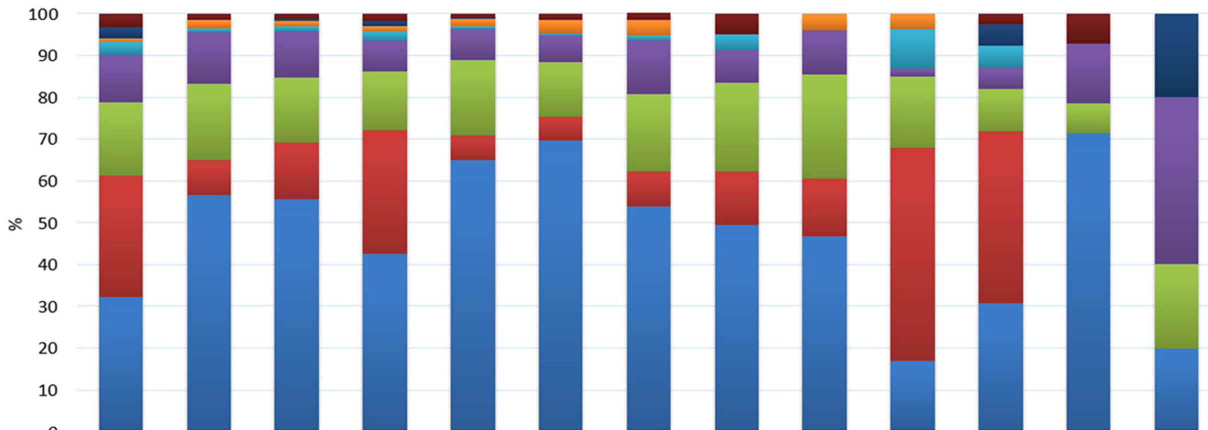
TABLE 1 Species distribution of *Candida* isolates over 5 years

	Overall		Yr 1		Yr 2		Yr 3		Yr 4		Yr 5	
***Candida* species**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Candida albicans	3,965	44.9	284	38.6	556	48.9	704	47.4	1,051	43	1,370	45.3
C. parapsilosis complex	1,762	20	172	23.4	184	16.2	241	16.2	538	22	627	20.7
C. parapsilosis sensu stricto	1,526	17.3	142	19.3	161	14.2	202	13.6	460	18.8	561	18.5
C. metapsilosis	167	1.9	23	3.1	14	1.2	25	1.7	54	2.2	51	1.7
C. orthopsilosis	35	0.4	4	0.5	7	0.6	6	0.4	12	0.5	6	0.2
Lodderomyces elongisporus	34	0.4	3	0.4	2	0.2	8	0.5	12	0.5	9	0.3
C. tropicalis	1,515	17.2	122	16.6	218	19.2	267	18	413	16.9	495	16.4
C. glabrata complex	955	10.8	90	12.2	115	10.1	178	12	260	10.6	312	10.3
C. glabrata sensu stricto	941	10.7	88	12	115	10.1	176	11.8	254	10.4	308	10.2
C. nivariensis	13	0.1	2	0.3			1	<0.1	6	0.2	4	0.1
C. bracarensis	1	<0.1					1	<0.1				
C. guilliermondii	186	2.1	12	1.6	16	1.4	20	1.3	53	2.2	85	2.8
C. krusei	125	1.4	18	2.4	16	1.4	24	1.6	25	1	42	1.4
C. pelliculosa	123	1.4	13	1.8	10	0.9	12	0.8	39	1.6	47	1.6
C. lusitaniae	50	0.6	6	0.8	4	0.4	18	1.2	12	0.5	10	0.3
C. lipolytica	36	0.4	9	1.2	3	0.3	5	0.3	10	0.4	9	0.3
C. haemulonii	24	0.3	1	0.1	3	0.3	6	0.4	10	0.4	4	0.1
C. intermedia	20	0.2			3	0.3	3	0.2	12	0.5	2	<0.1
C. norvegensis	13	0.1	1	0.1			3	0.2	6	0.2	3	0.1
C. fabianii	11	0.1	1	0.1			3	0.2	7	0.3		
C. inconspicua	8	<0.1			2	0.2			3	0.1	3	0.1
C. rugosa	7	<0.1			1	<0.1	1	<0.1	1	<0.1	4	0.1
C. fermentati	6	<0.1			2	0.2			2	<0.1	2	<0.1
C. quercitrusa	4	<0.1	3	0.4	1	<0.1						
C. catenulata	4	<0.1	2	0.3	1	<0.1			1	<0.1		
C. aaseri	3	<0.1									3	0.1
C. famata	3	<0.1	1	0.1					1	<0.1	1	<0.1
C. kefyr	3	<0.1	1	0.1							2	<0.1
C. opuntiae	1	<0.1			1	<0.1						
C. freyschussii	1	<0.1			1	<0.1						
C. magnoliae	1	<0.1									1	<0.1
C. palmioleophila	1	<0.1					1	<0.1				
C. utilis	1	<0.1									1	<0.1
C. diddensiae	1	<0.1									1	<0.1
Total	8,829	100	736	100	1,137	100	1,486	100	2,444	100	3,026	100

(25.2% versus 13.0%, $P < 0.01$) (Fig. 2). The frequency between blood source and non-blood source isolates was similar for *C. tropicalis* (28.9% versus 16.9%, $P > 0.05$) and the *C. glabrata* complex (11.5% versus 10.3%, $P > 0.05$). In addition, over the 5 years of the study, the *C. parapsilosis* complex was recovered at a higher frequency than *C. albicans* and became the most predominant species among isolates causing candidemia in years 1 and 4. Significantly higher proportions of *C. parapsilosis* complex isolates were also observed in CVC (29.6%) and peritoneal dialysate (50.9%) specimens compared with this species' average frequency (20%) ($P < 0.01$ for both comparisons) (Fig. 2). Of the uncommon *Candida* species, some were found in higher proportions in blood culture specimens than in non-blood culture specimens, e.g., *Candida guilliermondii* (3.1% versus 1.3%, $P < 0.01$), *Candida pelliculosa* (2.7% versus 0.4%, $P < 0.01$), and *Candida lipolytica* (0.8% versus 0.1%, $P < 0.01$).

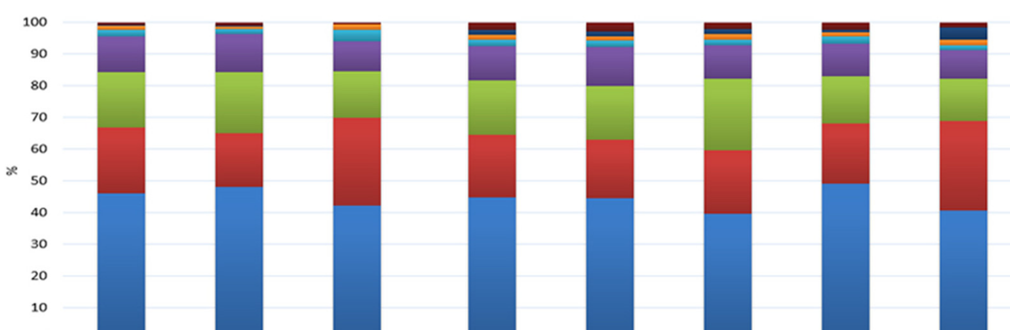
Species distribution by patient location and geographic regions. Of the *Candida* isolates recovered, 93.5% were from hospital inpatients (including those in intensive care units [ICUs] [31.4%], medical wards [20.4%], and surgical wards [32.9%]) and 6.5% were from patients in outpatient/emergency settings (Fig. 2). In all cases, *C. albicans* was the predominant species (39.7% to 49.3%). The second and third most common species in different clinical settings were either the *C. parapsilosis* complex or *C. tropicalis* (13.3% to 28.2%). The *C. glabrata* complex was the fourth most common

A. Distribution of *Candida* pathogens by specimen type



		Blood	Ascitic fluid	Pus	CVC	Bile	BALF	Pleural fluid	CSF	Tissue	Peritoneal dialysate	Hydrarthrosis	Gastric juice	Bone marrow
No. isolates		3858	1840	916	709	407	359	343	162	124	53	39	14	5
% of total		43.7	20.8	10.4	8.0	4.6	4.1	3.9	1.8	1.4	0.6	0.4	0.2	0.1
% of	*C. albicans*	32.3	56.5	55.7	42.5	64.9	69.6	53.9	49.4	46.8	17.0	30.8	71.4	20.0
	C. parapsilosis complex	28.9	8.5	13.5	29.6	6.1	5.8	8.5	13.0	13.7	50.9	41.0		
	C. tropicalis	17.5	18.2	15.4	14.1	17.9	13.1	18.4	21.0	25.0	17.0	10.3	7.1	20.0
	C. glabrata complex	11.5	12.4	11.1	7.3	7.4	6.4	12.8	8.0	10.5	1.9	5.1	14.3	40.0
	C. guilliermondii	3.1	1.0	1.2	2.4	0.7	0.3	1.2	3.7		9.4	5.1		
	C. krusei	0.8	1.8	1.4	1.0	1.7	3.3	3.8		4.0	3.8			
	C. pelliculosa	2.7	0.1	0.4	1.3	0.2						5.1		20.0
	Other spp.	3.2	1.5	1.2	1.8	1.0	1.4	1.5	4.9			2.6	7.1	

B. Distribution of *Candida* pathogens by clinical service



Species		Outpatient/ emergency	Emergency	Outpatient	Inpatient	Intensive care unit	Medical department	Surgical department	Other department
No. isolates		576	370	206	8253	2771	1804	2906	772
% of total		6.5	4.2	2.3	93.5	31.4	20.4	32.9	8.7
% of	*C. albicans*	46.0	48.1	42.2	44.8	44.5	39.7	49.3	40.8
	C. parapsilosis complex	20.8	17.0	27.7	19.9	18.6	20.1	18.8	28.2
	C. tropicalis	17.5	19.2	14.6	17.1	16.9	22.6	15.0	13.3
	C. glabrata complex	11.3	12.2	9.7	10.8	12.3	10.4	10.1	8.9
	C. guilliermondii	2.1	1.4	3.4	2.1	2.1	1.8	2.5	1.6
	C. krusei	1.2	0.8	1.9	1.4	1.3	1.9	1.1	1.8
	C. pelliculosa	0.2	0.3		1.5	1.4	1.4	1.0	3.8
	Other spp.	0.9	1.1	0.5	2.3	3.0	2.1	2.1	1.6

FIG 2 Distribution of *Candida* pathogens by specimen type (A) and clinical service (B). Abbreviations: BALF, bronchoalveolar lavage fluid; CSF, cerebrospinal fluid; CVC, central venous catheter.

species in all clinical settings (prevalence, 8.9% to 12.3%). Other *Candida* species were rare (<4%; Fig. 2).

Geographic variation in the species distribution was observed. For instance, *C. albicans* was most common in 57 of 65 (87.7%) hospitals, but its frequency varied widely from 12.5% to 100% in different hospitals. In the eight hospitals where

TABLE 2 *In vitro* susceptibilities of *Candida* spp. to fluconazole and voriconazole as determined by CLSI disk diffusion method

	Fluconazole[a]				Voriconazole[a]					
	S		R		S/WT		R/NWT		Cross-resistant	
Species	No.	%	No.	%	No.	%	No.	%	No.	%
C. albicans	3,927	99.0	20	0.5	3,928	99.1	30	0.8	19	0.5
C. parapsilosis complex	1,600	90.8	94	5.3	1,710	97.0	44	2.5	44	2.5
C. parapsilosis sensu stricto	1,425	93.4	61	4.0	1,485	97.3	34	2.2	34	2.2
C. metapsilosis	117	70.1	23	13.8	166	99.4	1	0.6	1	0.6
C. orthopsilosis	24	68.6	10	28.6	25	71.4	9	25.7	9	25.7
L. elongisporus	34	100			34	100				
C. tropicalis	1,285	84.8	202	13.3	1,295	85.5	200	13.2	195	12.9
C. glabrata complex			179	18.7	814	85.2	141	14.8	134	14.0
C. glabrata sensu stricto			179	19.0	800	85.0	141	15.0	134	14.2
C. nivariensis					13	100				
C. bracarensis					1	100				
C. guilliermondii	71	38.2	54	29.0	157	84.4	23	12.4	23	12.4
C. krusei			125	100	118	94.4	4	3.2	4	0.3
C. pelliculosa	68	55.3	24	19.5	102	82.9	12	9.8	12	9.8
C. lusitaniae	48	96.0			50	100				
C. lipolytica	6	16.7	25	69.4	24	66.7	12	33.3	12	33.3
C. haemulonii	5	20.8	18	75.0	15	62.5	9	37.5	9	37.5
C. intermedia	18	90.0	2	10.0	20	100				
C. norvegensis	3	23.1	7	53.8	13	100				
C. fabianii	11	100			11	100				
C. inconspicua	1	12.5	7	87.5	8	100				
C. rugosa	3	42.9	4	57.1	7	100				
C. fermentati	4	66.7	2	33.3	6	100				
C. catenulata			3	75.0	1	25.0	3	75.0	3	75.0
C. quercitrusa			3	75.0	4	100				
C. aaseri	2	66.7			3	100				
C. kefyr	3	100			3	100				
C. famata	2	66.7	1	33.3	3	100				
C. magnoliae			1	100	1	100				
C. utilis	1	100			1	100				
C. diddensiae			1	100			1	100	1	100
C. palmioleophila			1	100			1	100	1	100
C. opuntiae			1	100	1	100				
C. freyschussii	1	100			1	100				
Total	7,059	80.0	774	8.8	8,296	94.0	480	5.4	457	5.2

[a]Species-specific MIC clinical breakpoint (CBP) interpretive criteria were applied to *C. albicans*, *Candida tropicalis*, the *C. parapsilosis* complex, the *Candida glabrata* complex, and *Candida krusei* according to the guidelines in the reference CLSI M60 document (17), and the susceptibilities of the other *Candida* species were interpreted in accordance with CLSI M44-S3 document guidelines (18). S, susceptible; WT, wild type; R, resistant; NWT, non-wild type.

C. albicans was not the dominant species, the most common species were the *C. parapsilosis* complex, *C. tropicalis*, and *C. pelliculosa* in four hospitals, three hospitals and one hospital, respectively.

***In vitro* susceptibilities.** Of 8,829 *Candida* isolates, 80.0%, 11.2%, and 8.8% of the isolates were susceptible, susceptible dose-dependent (SDD), and resistant to fluconazole, respectively (Table 2). In comparison, 94.0% of isolates were susceptible to voriconazole or of the wild-type (WT) phenotype, 0.6% were SDD or intermediate, and 5.4% were resistant or non-wild-type (NWT) (Table 2). Cross-resistance occurred in 5.2% (457/8,829) of the isolates (Table 2), and 59.0% (457/774) of fluconazole-resistant isolates were azole cross-resistant. Across the different hospitals, the fluconazole and voriconazole susceptibility rates ranged from 50% to 100% and 43% to 100%, respectively.

Among the common *Candida* species, >99% of *C. albicans* isolates were susceptible to both fluconazole and voriconazole (Table 2), as were *C. parapsilosis* complex isolates. However, within the *C. parapsilosis* complex, 13.8% of the *C. metapsilosis* isolates were fluconazole resistant, whereas the rate was 4.0% among *C. parapsilosis sensu stricto* isolates ($P < 0.01$); *C. orthopsilosis* isolates also had a high frequency of resistance to both fluconazole (28.6% versus 4.0% for *C. parapsilosis sensu stricto* isolates, $P < 0.01$)

and voriconazole (25.7% versus 2.2% for *C. parapsilosis sensu stricto* isolates, $P < 0.01$). Other species that accounted for >2% of the collection, including *C. tropicalis*, the *C. glabrata* complex, and *C. guilliermondii*, had higher rates of fluconazole resistance (>13%), voriconazole resistance (>12%), and azole cross-resistance (>12%) than *C. albicans* and the *C. parapsilosis* complex (Table 2). For *C. krusei*, 94.4% of isolates were susceptible to voriconazole (Table 2). The overall fluconazole resistance rate for other rare *Candida* species reached up to 31.2% (100/321), and the voriconazole resistance rate was 11.8% (38/321).

Trends of fluconazole and voriconazole resistance over 5 years. Over the 5-year study period, the overall fluconazole susceptibility rates were 81.0%, 85.0%, 81.2%, 78.1%, and 78.7%, respectively, and the voriconazole susceptibility/WT rates were 94.2%, 96.5%, 95.0%, 93.4%, and 92.9% respectively. *C. albicans* remained highly susceptible to both azoles over 5 years (susceptibility rate > 98%) (Fig. 3). The fluconazole susceptibility rate of *C. parapsilosis* complex isolates significantly decreased from 98.8% in the first year to 86.2% in the fourth year ($P < 0.01$), although it climbed back to 90.6% in the fifth year (Fig. 3A), while in contrast, the rates of susceptibility to voriconazole remained similar (>95.0% of isolates were susceptible; Fig. 3B). Similar trends were found for the *C. glabrata* complex (the fluconazole resistance rate increased from 12.2% to 24.0%, $P < 0.01$) (Fig. 3A), but the proportion of isolates WT for susceptibility to voriconazole remained at 82.2% to 88.8% (Fig. 3B).

However, the susceptibility of *C. tropicalis* to both fluconazole and voriconazole decreased continuously, from 94.3% (for both azoles) in year 1 to 76.2% and 76.8%, respectively, in year 5 ($P < 0.01$ for both comparisons) (Fig. 2A and B). In addition, the fluconazole susceptibility rate of *C. guilliermondii* dropped from 100% to 37.6% ($P < 0.01$) (Fig. 3A), and its voriconazole susceptibility rate decreased from 100% to 89.4% ($P < 0.01$) (Fig. 3B). *C. pelliculosa* and other rare *Candida* species exhibited generally high rates of resistance to fluconazole and voriconazole, but no significant trends were observed (Fig. 3).

DISCUSSION

This large study has provided valuable data to inform the management of IC in Chinese hospitals. As expected, the four major *Candia* pathogens, *C. albicans*, the *C. parapsilosis* complex, *C. tropicalis*, and the *C. glabrata* complex, accounted for 92.9% of isolates and predominated in all hospitals except one. Generally, *C. albicans* remained the most common species, and no trends toward a decrease in frequency were observed over the 5 years. In addition, the species was susceptible to both fluconazole and voriconazole, which was comparable to global data obtained during the same time period (>99% susceptibility rates) (3, 19–21). *C. albicans* accounted for 44.9% of the isolates collected in this study, which is similar to the prevalence in North America, Latin America, and other regions in the Asia-Pacific region (40% to 45%) but lower than that in Europe (>50%) (20–22). Of note, the prevalence of *C. albicans* in the Asia-Pacific region has decreased by about 20% compared with that determined from data obtained from 2001 to 2007 (23). The proportion of *C. albicans* isolates as the causative agent among candidemia cases was even lower (32.3%).

On the other hand, the overall frequency of non-*albicans Candida* species as a cause of IC was high in China, with the members of the *C. parapsilosis* complex being the second most predominant species in this study (20%). Of note, this frequency was even higher than that of *C. albicans* among candidemia patients in year 1 (8) and year 4. *C. parapsilosis* complex isolates are notable for their ability to adhere to catheters and other medical devices, to develop biofilms, and to colonize human skin, all of which may facilitate nosocomial outbreaks (1, 12, 24). A reassuring finding was that azole resistance (<6%) was uncommon in the present study, similar to global surveillance data (0 to 5.4%) (3, 19, 21). However, differences in azole resistance rates were noted among the different species within the *C. parapsilosis* complex, with *C. metapsilosis* and *C. orthopsilosis* showing the highest rates of resistance, as has been reported in previous studies (25, 26).

C. tropicalis was the third most common species in the study (17.2%). Of note, this species has become one of the more common non-*albicans Candida* species worldwide,

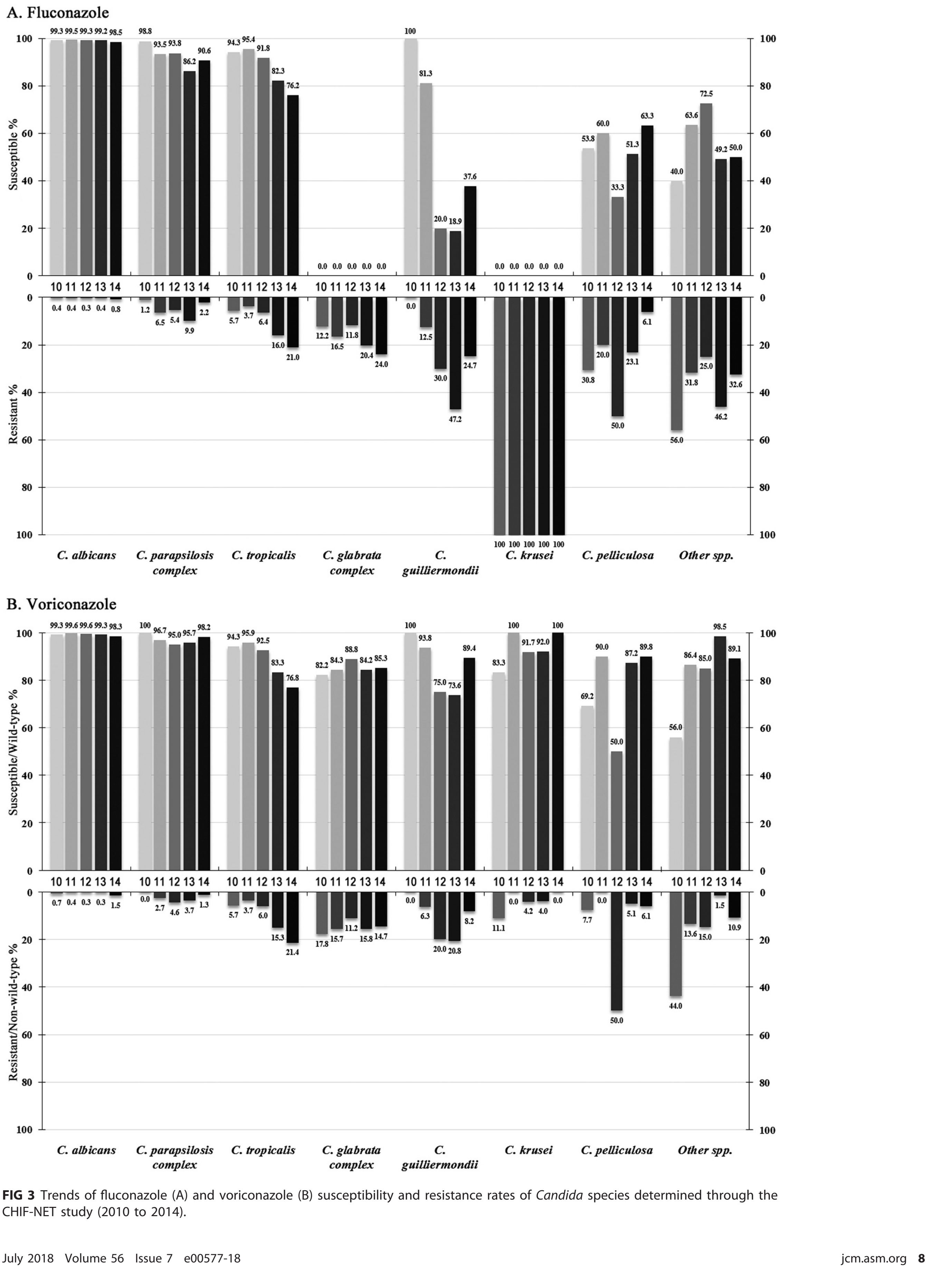


FIG 3 Trends of fluconazole (A) and voriconazole (B) susceptibility and resistance rates of *Candida* species determined through the CHIF-NET study (2010 to 2014).

and its prevalence in Latin America (13% to 18%) and the Asia-Pacific region (about 12%) is generally higher than that in North America (7% to 9%) and Europe (4% to 9%) (20, 23). There is a general consensus that *C. tropicalis* strains may exhibit a moderate level of azole resistance. Resistance rates have remained stable in North America and Europe (generally, $<$10%) (20, 21, 27). However, in the present study, a notable trend of increasing rates of azole resistance among *C. tropicalis* isolates was observed in China ($<$6% in year 1 to $>$20% in year 5). This was also observed using data obtained by the broth microdilution method from 10 hospitals which consistently participated in the CHIF-NET study over the 5-year period (13). In addition, a higher azole cross-resistance rate was observed in *C. tropicalis* isolates (96.5%) than in *C. parapsilosis* complex (46.8%) and *C. glabrata* complex (74.9%) isolates. Worldwide, azole resistance in *C. tropicalis* has been mainly noted in the Asia-Pacific region (3, 13, 28), whereas azole resistance rates among *C. tropicalis* isolates in North America or European countries remain low ($<$10%) (3, 23, 29). As *C. tropicalis* infection is associated with higher rates of mortality and more adverse outcomes (30), consideration may be given to the use of echinocandins as first-line agents in treating *C. tropicalis* infections in China.

C. glabrata complex isolates accounted for 10.8% of the collection in the present study, similar to the situation in Europe (10% to 16%) but less than that in the United States, where *C. glabrata* was the most common non-*albicans Candida* species (20% to 26%) (20, 21, 23). This species is well-known for its high rates of azole resistance, mainly due to the upregulation of drug transporters and the overexpression or alteration of the drug target (2, 4). In this study, the rate of fluconazole resistance among the isolates was 18.7%, which is a rate higher than the global average (8% to 16%) (3, 20, 21, 23). Moreover, 14.0% of isolates were cross-resistant to both fluconazole and voriconazole. A significant increase in the rate of fluconazole resistance in *C. glabrata* complex isolates was observed over the 5 years of this study, and this has also been noted using broth microdilution methods in hospitals which consistently participated in the CHIF-NET study (14).

Other *Candida* species, although uncommon, exhibited high fluconazole (44.1%) and voriconazole (10.3%) resistance rates. In addition, many of the less common species that were highly resistant to fluconazole, e.g., *C. pelliculosa* and *C. lipolytica*, were more commonly isolated from blood samples than non-blood sources. However, less common *Candida* species were more likely to be misidentified by phenotypic and biochemical-based identification methods (8, 15, 31). Although MALDI-TOF MS has good accuracy, its capacity to identify an ever expanding range of pathogens largely relies on its protein mass spectral database (15, 32, 33). The CHIF-NET study has also provided a valuable isolate repository including more novel or uncommon species that may be used to expand and build local MALDI-TOF MS identification databases (11, 31, 34) for future surveillance.

There were several limitations in our study. First, the study employed the CLSI disk diffusion assay for antifungal susceptibility testing. The methodology was developed and verified in the 10.5-year ARTEMIS global surveillance program, and the results of that methodology showed a good correlation with those of the "gold standard" broth microdilution method (9, 23). However, to date, azole species-specific CBPs of the disk diffusion method are available only for the most common *Candida* species, i.e., *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei* (17), and the use of old non-species-specific CBPs (18) for other *Candida* species may introduce incorrect interpretations of the isolates' susceptibilities. Building up epidemiological cutoff values for less common *Candida* species in China is the next-step goal of the program. In addition, the antifungal agents tested in the present study were limited to only two azoles. However, with the increasing prevalence of azole-resistant *Candida* isolates, echinocandins have become the first-line treatment of IC (4, 14, 24). In mainland China, echinocandin-nonsusceptible *C. glabrata* cases have also been identified (9, 14). To address these limitations, we envisage performing broth microdilution to examine the susceptibilities to a broader range of antifungal agents for the next 5 years of the CHIF-NET surveillance study (year 6 to year 10). Moreover, further investigations on antifungal resistance mechanisms, e.g., mutations in the *ERG11* and *FKS* genes and overexpression of drug efflux pumps (2, 4, 29), would enhance the value of the *in vitro* susceptibility results. Another potential limitation is that there were disparities between the numbers of isolates collected from different provinces, which may influence the accurate geographic picture of the species distribution or antifungal resistance. In order to obtain more representative regional IC data with less bias, the CHIF-NET Study Group has now established subsidiary surveillance programs in each province of China (35).

In conclusion, this study has provided useful data on the epidemiology of IC in mainland China. Although *C. albicans* remained the most common species, non-*albicans Candida* species were responsible for about 55% of cases of IC and over 67% of candidemia cases. Fluconazole and azole cross-resistance rates were notably high in *C. tropicalis* and *C. glabrata*, and their fluconazole resistance rates increased significantly over the 5 years. Less common *Candida* species also exhibited high fluconazole resistance rates, and molecular or mass spectrum methods were essential for the identification of uncommon species. Antifungal resistance has become a threat, and continued surveillance is still warranted.

ACKNOWLEDGMENTS

The co-principal investigators in the 65 hospitals participating in the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study Group (CHIF-NET 2010 to 2014) are as follows: (1) Ying-Chun Xu and He Wang, Peking Union Medical College Hospital, Beijing; (2) Mei Kang and Yu-Ling Xiao, West China Hospital of Sichuan University, Chengdu, Sichuan Province; (3) Zi-Yong Sun and Zhong-Ju Chen, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province; (4) Kang Liao and Peng-Hao Guo, The First Affiliated Hospital of Zhongshan University, Guangzhou, Guangdong Province; (5) Yan-Ping Luo and Li-Yan Ye, The General Hospital of People's Liberation Army, Beijing; (6) Zhi-Dong Hu and Na Yue, General Hospital of Tianjin Medical University, Tianjin; (7) Ya-Ning Mei and Gen-Yan Liu, Jiangsu Province Hospital, Nanjing, Jiangsu Province; (8) Da-Wen Guo and Shu-Lan Chen, The First Clinic College of Harbin Medical University, Harbin, Heilongjiang Province; (9) Ruo-Yu Li and Zhe Wan, Peking University First Hospital, Beijing; (10) Yu-Hong Pan and Lan-Mei Gao, Fujian Medical University Union Hospital, Fuzhou, Fujian Province; (11) Yun-Zhuo Chu and Fu-Shun Li, First Hospital of China Medical University, Shenyang, Liaoning Province; (12) Yun-Song Yu and Jie Lin, Sir Run Run Shaw Hospital, Hangzhou, Zhejiang Province; (13) Xian-Ju Feng and Hui Xu, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province; (14) Qing Yang, The First Affiliated Hospital of the Zhejiang University School of Medicine, Hangzhou, Zhejiang Province; (15) Hai-Feng Shao, General Hospital of Nanjing Military Area Command, Nanjing, Jiangsu Province; (16) Wen-En Liu and Hong-Ling Li, Xiangya Hospital, Central South University, Changsha, Hunan Province; (17) Huo-Xiang Lv and Qu-Hao Wei, Zhejiang Province People's Hospital, Hangzhou, Zhejiang Province; (18) Yong Wang and Yan Jin, Shandong Provincial Hospital, Qingdao, Shandong Province; (19) Li-Wen Liu, The People's Hospital of Liaoning Province, Shenyang, Liaoning Province; (20) Dan-Hong Su, The First Affiliated Hospital of Guangzhou Medical Collage, Guangzhou, Guangdong Province; (21) Yu-Xing Ni, Shanghai Ruijin Hospital, Shanghai; (22) Gui-Ling Zou and Xue-Fei Du, The Fouth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province; (23) Xin-Lan Hu and Ning Li, Fujian Provincial Hospital, Fuzhou, Fujian Province; (24) Ling Ma and Shuai-Xian Du, Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei Province; (25) Xiu-Lan Song, The First Hospital of Jiaxing, Jiaxing, Zhejiang Province; (26) Hua Yu and Xiang-Ning Huang, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, Sichuan Province; (27) Tie-Li Zhou and Qing Wu, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province; (28) Wei-Jia and Gang Li, The General Hospital Affiliated to Ningxia Medical University, Yinchuan, Ningxia Province; (29) Qiang-Qiang Zhang, Huashan Hospital, Fudan University, Shanghai; (30) Zhi-Jie Zhang, The Second Hospital Affiliated to China Medical University, Shenyang, Liaoning Province; (31) Zhi-Yong Zhang, Southwest Hospital Affiliated to the Third Military Medical University, Chongqing; (32) Rong Zhang and

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This work was supported by the Peking Union Medical College Hospital Outstanding Young Talents Program (JQ201703), the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2016-I2M-1-014), and the Beijing Innovation Base Cultivation and Development Special Fund (Z171100002217068).

We declare no conflict of interests.

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